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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,969	09/11/2000	Winfried Edelmann	AHN-001DV2	5790

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/658,969	Applicant(s) EDELMANN ET AL.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17 and 22-31* is/are pending in the application.

4a) Of the above claim(s) *24 and 26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17,22,23,25,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of the invention of Group II, claim 25 and 15-17, 22, 23, 30 and 31 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that all the methods employing compounds recited herein are not independent. This is not found persuasive because. Inventions can be shown to be independent if they have different functions, effects, or modes of operation. In the instant case, they are independent and distinct because they have different modes of operation. For example, each invention group operates by employing different patentably distinct compounds. These compounds are classified into vastly different classification, which indicate that they are recognized in different, distinct, and separate status of art. The search for all the invention encompassed by the claims will therefore impose an undue burden to the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-17 and 22-31 are pending. Claims 24, 26-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. The references cited in the PTO-1449 form filed January 29, 2001 have not been considered since no reference is provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17, 22, 23, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification fails to provide a written description of what a small molecule that has a function of modulating MSH5 expression would be. Throughout the instant specification, only three places mention the term "small molecules" (page 8, line 5, page 14, line 32, and page 15, line 23). No small molecules are exemplified. In fact, there is only description of what the small molecules can do (i.e., modulating the expression of MSH5) and no description of what these small molecules are.

Claims 22, 23, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the instant case, attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention; 2) the breath of the claims; 3) the predictability of unpredictability of the art; 4) the amount of direction or guidance presented; 5) the

presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art; and 8) the state of the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) The nature of the invention

Claims 15,16 and 31 are directed to a method for modulating MSH5 function or MSH5 expression using a compound binding to MSH5; Claims 17 and 22 are directed to applying the said method to infertility (contraception).

2) The breadth of the claims (the scope of the claims)

The specification and claims do not disclose one reasonable method for the utilization of the small molecule compounds that encompasses numerous and unpredictable variant molecules to modulate MSH5 activities and expression in cell and to target MSH5-related infertility. Moreover, the instant claims do not disclose characteristics/attribute of the MSH5 activity that is fundamentally important for the modulation by MSH5 interacting compound(s). Thus, employing numerous and unpredictable candidate compounds to target undisclosed MSH5 "activity" would result in encompassing all possible approaches of modulation of MSH5 function and expression and related fertility disorder thereby. This would render the result of the method using the same is unpredictable and would render the claims so broad that the scope of the claims is out of the scope of the instant application.

3) The unpredictability

There are an unpredictable diversity of using the numerous and unpredictable compound(s) of specific and non-specific and different degree of affinities of the compound(s) for MSH5 protein and MSH5 functional unit(s) (e.g. in vivo existing hetero-oligomer). Thus, the result is highly variant of modulation of MSH5 activity or MSH5 expression in cell, and the result is also hightly variant of targeting MSH5-related infertility based on the same (see the foregoing statement). Overall, the invention is unpredictable in the absence of factual indicia to the contrary.

4) The amount of direction or guidance presented

The instant specification does not provide any method specifically of/and detailed for using MSH5 interacting compound for modulating MSH5 activities or MSH5 expression in cell, and for MSH5-targeted infertility. The disclosure lacks guidance/direction as to (i) how to ascertain suitable small molecule compounds used in the herein claimed invention, (ii) what MSH5 activities is/are affected, (iii) with respect to any combination of (i) and (ii), how MSH5 expression or MSH5 per se is regulated with reasonable outcome without undue experimentation.

The specification does not provide any specific guidance as to how one skilled in the art would have selected and used the MSH5 regulation compound(s) in the claimed method.

On page 8, the specification defines the "small molecules" as any agent, which "bind to MSH5 proteins"; yet, there no further description with respect to the compound,

i.e. "modulator (see page "screening assay" page 14, lines 30-35). It noted that the specification fails to define what a "small molecule" is. How small is small? Such term represents compounds encompassing vastly different and distinct molecules from small molecule (e.g. H_2O), antisense molecules, and any unknown compounds that binds to MSH5, nucleotides (e.g. nucleoside triphosphates including ATP, ADP and ATP analogues, ATP-PNP, ATP-PCP, etc.), polynucleotides including any DNA chains containing MSH5 binding site(s) from the species of cells. The number of the compounds is further magnified by the following parameters.

(i) MSH5 forming hetero-oligomeric characteristics (see Prochart, P. et al. (1997) J. Biol. Chem. Vol. 272, 30345-30349); therefore, MSH5 can interact with ligands or substrates through the hetero-oligomer(s);

(ii) Non-specific binding MSH5 (note that the specification does not sets forth the affinity of binding specifically), therefore, the number of molecules interacting with MSH5 is unpredictable;

(iii) Any naturally-occurring mutations and genetic-engineering generated mutations in the DNA fragments that interact with MSH5 or MSH5 hetero-oligomers; there fore the number of molecules interacting with MSH5 is unpredictable and without upper limit; and

(iv) Affinity of the binding (note that in the specification there are nowhere characterization and exemplification with regard to affinity of any compounds interaction with MSH5), there fore there is no lower limit for the said binding to any compounds.

In light of the parameters (i) – (iv), any combination of them would encompass numerous variants of small molecule compounds, in which are unpredictable and unknown to one of skilled in the art.

Moreover the specification is silent as to the activity of MSH5 protein. The specification does not provide any guidance and demonstration of assay the MSH5 activity and of how this activity is modulated by the compound(s) and what is the activity related to infertility.

MSH5 has biochemical properties (a) ability of nucleotide binding (e.g. bind ATP and ADP etc.), (b) ability of formation of hetero-oligomer with other MutS proteins (MSH1-6, especially forming hetreodimer in vivo MSH5/MSH4); (c) ability of hydrolyzing ATP (ATPase activity); and (d) ability of recognizing and binding to DNA fragments involved in crossovers between homologous chromosomes of mitosis (Prochart, P. et al. (1997) J. Biol. Chem. Vol. 272, 30345-30349 and Fishel, R. A. et al. US Patent 6,333,153)). The disclosure of the present invention does neither describe what MSH5 activity is attributed to the claimed method nor provide direction/guidance as to how the activity is modulated by the compound.

In addition, the specification and claims do not provide ant specific guidance on the degree of variant compounds permitted in modulation of MSH5 biological function and of MSH5 expression in transgenic animals, and in use as infertility (contraceptive) agents. Since the disclosure fails to describe common attribute and characteristics that identify a compound in modulating MSH5 activities as mentioned in the foregoing statement, one of skilled artisan is require to perform undue experimentation in order to

determine appropriate compound(s) to target a MSH5 activity in the process of MSH5 functional modulation and MSH5celluilar expression regulation as well as in the process of MSH5-related fertility disorder.

Because the present invention is directed to use of MSH5 interacting agent *in vivo* and because the functional unit *in vivo* for MSH5 is at least heterodimer (e.e. MSH4/MSH5), any mutatants, antisense molecules, or fragments derived from MSH4 or other MutS proteins that interact with MSH5 would also be potential ligands for binding to MSH5 (wild type per se). Since the modulation of MSH4 activity or function is at least in part dependent of heterodimer activity, given the mutational variants of MSH4 (a MSH5 cognate and acting as ligands to MSH5 hereof) require direction, absent specific detailed guidance, practicing the claimed method of modulating MSH5 activity or expression in vivo would require undue experimentation.

5) The presence or absence of working examples

The specification provides no example as to (a) a compound of being capable of interaction with MSH5 or/and negatively regulating MSH5 biological activity, i.e., inhibition; (b) a sufficient concentration of the compound that inhibits MSH5 and its cellular expression; (c) how the compound regulate MSH5 protein function in vivo (note that the present invention sets forth preferred use of MSH5 transgenic mice and all exemplary embodiment descriptions is directed to the same); (d) how to apply the said method based on utilization of the compound(s) to contraception (infertility); and (e) what and how MSH5 is related to the claimed MSH5 cellular expression and accordingly

to the compound mediated MSH5 regulation in cell. All the above mentioned issues (a) – (e) constitute the subject matter of the present invention.

In the absence of working examples with regard to the above mentioned numerous variant sequences, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trial and error to practice the claimed invention. Because of the reasons forgoing, the quantity of experimentation would be large and unpredictable because the skilled artisan would have been required to carry out a large body of tests for screening and making any small molecule compound(s) that is (are) of desirable inhibitory activities against MSH5 without a prior expectation of success.

6) The quantity of experimentation necessary

Because of the unpredictability and the unknown structures of small molecules that encompassed by the claims, the number of experiments needs to be done in order to ascertain the appropriate small molecule compounds would be enormous.

7) The relative skill of those in the art

The general knowledge and level of skill in the art a Ph.D. with several years of experience do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide. In view of the preceing factors (1-5), the level of skill in this art is high and requires at least an organic chemist or a biochemist with several years of experience in protein manufacturing as well as knowledge in organic

synthesis art, peptide chemistry, enzymology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

8) The state of the art

The state of the art is that there is no known "small molecules" or chemical entities that is able to specific modulate a particular gene expression.

In consideration of each of factors stated above, there is undue experimentation because of variability in prediction of outcome that is not addressed by the instant application disclosure, examples, and teaching. Absent factual data to the contrary, one skilled in the art would need to perform undue experimentation in order to ascertain the appropriate embodiments for practicing the herein claimed invention.

In view of the above, the claims are properly rejected under 35 USC 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-17, 22, 23, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "compound" in claim 15 renders the claim indefinite as to what compounds are encompassed by the claims. Only functional language is recited.

Therefore, one of ordinary skill in the art would not know what compounds are or not fall into the scope of the herein claims.

The expression "sufficient concentration" in claim 15 renders the claims indefinite because the activity of MSH5 that is modulated is not clear to one of ordinary skill in the art. Therefore, it is not clear what concentration would be encompassed by the term "sufficient concentration".

Claim 22 is indefinite because it recites "said compound is a contraceptive agent", in which the said agent is neither disclosed in the specification nor in the claims and referred to any agent having activity that can be served as contraceptives.

The term "small molecules" in claim 25 is a relative term which renders the claim indefinite. The term "small molecules" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what compounds are considered "small molecules" to one of ordinary skill in the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 16, and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Fishel et al.

Fishel et al. teaches a process for modulating MSH5 protein activity by a binding solution comprising ATP and ADP, in a specific concentration, that can affect the activity of MSH5 (See col. 20, line33 - col. 21, line 10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 22, 23, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishel et al. as applied to claims 15-16 above, and further in view of Her et al. (Genomics, 1998;52:50-61) and Baker et al. (Nature Genetics, 1996;13:336-342).

Fishel et al. does not expressly teach the inhibition of MSH5 activity would be useful as contraceptive.

Her et al. teaches structural characterization of human MSH5 gene and suggest that expression of MSH5 and MSH5/MSH4, one of function heterodimers, in human testis involves in human infertility (See page 59, last paragraph of Discussion Section).

Baker et al. teaches the involvement of mouse MLH1 in both DNA mismatch and meiotic crossingover, and speculate that the fertility of MS-2-deficient mice raise the possibility that other MutS-like protein, MSH5, act in conjunction with MLH1 during meiosis (See page 341, col. 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the compounds of Fishel et al. to inhibit MSH5 and useful in the method of contraceptive thereby.

One of ordinary skill in the art would have been motivated to employ the compounds of Fishel et al. to inhibit MSH5 and useful in the method of contraceptive thereby since MSH5 is involved in meiotic crossing over, which is important in spermatogenesis. Inhibiting such process or the activity thereof, and to reduce the

spermatogenesis and employed such method for contraception thereby would be reasonably expected to be effective.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
January 7, 2003

RUSSELL TRAVERS
PRIMARY EXAMINER
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